AD_____

Award Number:

W81XWH-10-1-0898

TITLE:

Improving the Efficiency and Efficacy of Glibenclamide in Limiting Progressive Hemorrhagic Necrosis Following Traumatic Spinal Cord Injury

PRINCIPAL INVESTIGATOR: J. Marc Simard, M.D., Ph.D.

CONTRACTING ORGANIZATION:

University of Maryland, Baltimore
Baltimore, MD 21201

REPORT DATE:

October 2012

TYPE OF REPORT:

Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| 01/Oct/ 2012 | Annual | 09/30/11-09/29/12 |

**4. TITLE AND SUBTITLE**

Improving the Efficiency and Efficacy of Glibenclamide in Limiting Progressive Hemorrhagic Necrosis Following Traumatic Spinal Cord Injury

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**
W81XWH-10-1-0898

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
J. Marc Simard, M.D., Ph.D.

E-Mail: msimard@smail.umaryland.edu

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

University of Maryland, Baltimore

Baltimore, MD 21201

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

Preclinical work has demonstrated that glibenclamide administration improves outcomes in rat models of spinal cord injury, with the principal mechanism of action being amelioration of post-traumatic hemorrhagic necrosis (PHN). We hypothesize that some but not all patients with spinal cord injury, principally those with incomplete lesions, will respond to glibenclamide therapy. Our goal is identify early markers of injury that can be used to predict which patients may benefit from glibenclamide treatment. In this proposal, we will measure early biological markers of injury severity, specifically, serum biomarkers and T2 MRI findings obtained within hours of injury. We will subsequently correlate these early abnormalities with 6-month neurological examinations. During the first year of patient recruitment, we enrolled 6 patients. For the second year, the period 10/2011 through 10/2012, we enrolled 11 new patients. Five of the new patients have completed the entire 6 months study period. The remaining 6 patients are all scheduled for their 6 month final visit in January 2013.

**15. SUBJECT TERMS**
spinal cord injury, serum biomarkers, magnetic resonance imaging

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| U | U | U | UU | 5 | 19b. TELEPHONE NUMBER *(include area code)* |

**TABLE OF CONTENTS:**

## INTRODUCTION:

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The magnitude of acute post-traumatic hemorrhagic necrosis (PHN) is an early prognostic indicator of long-term functional recovery in human spinal cord injury (SCI). Recent preclinical data indicate that PHN can be reduced and functional recovery improved in spinal injured rats using glibenclamide, an FDA approved anti-diabetic drug that targets SUR1 receptors on endothelium and neurons. The range of injuries experienced by humans with SCI includes two major subclasses: (i) those that are neurologically complete within 24 hours post-injury and that are largely untreatable by available methods; (ii) those that are incomplete but are at risk to slowly evolve into complete lesions as a result of PHN. We hypothesize that only a subset of spinal cord injuries, principally those that are incomplete, will respond to glibenclamide therapy. In this proposal (the clinical portion of the overall proposal), we will examine this hypothesis. Specifically, T2 MRI will be used to measure acute hemorrhage and edema at sites of SCI across a range of human SCI patients with diverse neurological (ASIA) scores. Serum biomarkers will be analyzed. A correlation of ASIA scores at 6 months and MRI and biomarker panels obtained at 6-8 hrs will be used to assess how initial hemorrhage and select biomarkers predict long-term neurological recovery.

## BODY:

This section of the report shall describe the research accomplishments associated with each task outlined in the approved Statement of Work. Data presentation shall be comprehensive in providing a complete record of the research findings for the period of the report. Provide data explaining the relationship of the most recent findings with that of previously reported findings. Appended publications and/or presentations may be substituted for detailed descriptions of methodology but must be referenced in the body of the report. If applicable, for each task outlined in the Statement of Work, reference appended publications and/or presentations for details of result findings and tables and/or figures. The report shall include negative as well as positive findings. Include problems in accomplishing any of the tasks. Statistical tests of significance shall be applied to all data whenever possible. Figures and graphs referenced in the text may be embedded in the text or appended. Figures and graphs can also be referenced in the text and appended to a publication. Recommended changes or future work to better address the research topic may also be included, although changes to the original Statement of Work must be approved by the Army Contracting Officer Representative. This approval must be obtained prior to initiating any change to the original Statement of Work.

We have made important progress in patient enrollment. During the first year of patient recruitment, we enrolled 6 patients. Last year, we put into place some modifications that have helped to increase enrollment. For the second year, the period 10/2011 through 10/2012, we enrolled 11 new patients. Five of the new patients have completed the entire 6 months study period. The remaining 6 patients are all scheduled for their 6 month final visit in January 2013.

Enrollment continues to be challenging, for a variety of reasons:

- Several patients who might otherwise have been eligible were transferred from an outside facility and therefore could not be captured within the 8 hour enrollment window.

- We screened 5 elderly eligible patients, over the age of 70 years old, who are excluded because of age
- Three potential patients had a non-eligible cervical level lesion, C1 and C2 injuries

All efforts continue to be made to meet enrollment goals. We are actively screening for eligible patients "24/7". The research staff rotates a research dedicated cell phone that acts as a pager. All the neurosurgery residents have the cell phone number and we get called for all potential eligible patients. We work very closely with the neurosurgery residents; all are certified by IRB requirements to consent eligible patients because time is of essence.

Currently we have a total of 17 patients enrolled. Our goal is 30 patients.

To date, no analysis of the data has been carried out.

## KEY RESEARCH ACCOMPLISHMENTS:

Bulleted list of key research accomplishments emanating from this research.

→ good progress toward meeting enrollment goal
→ continued vigilance to make sure that no eligible patient is missed

## REPORTABLE OUTCOMES:

Provide a list of reportable outcomes that have resulted from this research to include: manuscripts, abstracts, presentations; patents and licenses applied for and/or issued; degrees obtained that are supported by this award; development of cell lines, tissue or serum repositories; infomatics such as databases and animal models, etc.; funding applied for based on work supported by this award; employment or research opportunities applied for and/or received based on experience/training supported by this award

→ none to date

## CONCLUSION:

Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

→ patient recruitment is proceeding well and is expected to continue apace.

## REFERENCES:

List all references pertinent to the report using a standard journal format (i.e. format used in *Science, Military Medicine*, etc.).

**None**